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Review paper

Natural products in green-detection of cancer cells, cancer therapy, and monitoring of therapeutic and cancer progression: A perspective

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Abstract

The natural products embedded with the molecular framework by combining with themselves or other molecules and biological micro/macro molecules. By the help of some special techniques, that can be incorporated to identify and detect different body markers as well as pathophysiological conditions. To date, a number of cancer detection methods are available. However, an early cancer detection is still remained the key problems, which causes delay, reduction of success rate in the cancer therapy, and increased the lethality, as cancer is a complicated and a large group of related diseases. To date, due to the promising biological compatibility and safety profile, many natural products have been used as anticancer drugs. Additionally, many of them are also included in the green syntheses, especially the plant-derived products. It is due their less or even non-toxic and economic character. This text offers a perspective on the detection of cancer by using natural products, along with a therapeutic and monitoring of treatment and cancer progression, suggests that, the natural products can be considered as leading tools in overall cancer management.

Keywords: *Biomarkers; Chemical Compounds; Cancer Detection.*

1. Introduction

Cancer, the general term usually describes a large group of related diseases. Our body is composed of trillions of cells. In a normal physiology all works together. At the beginning of cancer, one of them stops paying attention to the normal signals and/or may exert abnormal or altered functions and can tell cells to grow, stop growing or even to die. However, it shares almost the same needs and properties of normal cells, as it needs to survive and multiply in the same host, but becomes independent (Huda and Slone 1995; Segen and Wade 2002).

An early detection is one of the key problems in the treatment of cancer. Doubtless, cancer is detected in its later stages, and most often when it has compromised the function of one or more vital organ systems and is widespread throughout the body. Therefore, the early detection of cancer is of utmost importance in the proper diagnosis and treatment of each cancer, as the treatment plan is fully dependent on this fact. To date, a number detection method is available. However, no test is 100% accurate, as most of them according to their sensitivity and specificity result, false positive/false negative rates (Huda and Slone 1995; Segen and Wade 2002; Li et al. 2016).

Nowadays, the natural products (e.g. - plants, animals, microbes from terrestrial and marine environment origin) are being extensively used in many sectors, including food and beverages, cosmetics and toiletries, laboratory synthesis, treatment of diseases, and so on (Crotti et al. 2015; Islam et al. 2016). However, natural products can be used in the detection and diagnosis of diseases, especially the cancer (Chanda et al. 2011). This text offers a featuring hope, aiming to procure attention of the scientists to use natural products in the detection of cancer. Additionally, natural product-emphasized monitoring of therapeutic and cancer progression have been also depicted.

2. Natural products in the detection of cancer cells

Till date, a number of natural products have been marketed as anticancer drugs (Table 1).

Table 1: List of Natural Compounds Marketed for Anticancer Therapy

Sources	Lead compounds	Class
Bacteria	Bleomycins	Antibiotics
	Dactinomycin	
	Daunobicin	
	Doxorubicin	
	Mitomycin	
	Mitoxantrone	
Marine	Epothilones A-F	Epothilones
	Vorinostat	Histone deacetylase inhibitors
	Cytarabine	Marine products
	Trabectedin	
Plants	Camptothecin	Camptothecin analogs
	Etoposide	Epipodophyllotoxins
	Teniposide	
	Paclitaxel	Taxanes
	Retinol	Retinoids
	Vinblastine	Vinca alkaloids
	Vincristine	

In addition, there is an increasing interest arose in the production of semi-synthetic derivatives from natural active substances (lead

compounds) to improve the biological activity or to reduce the side effects. Examples of some marketed semi-synthetic anticancer drugs are: cabazitel, docetaxel, epirubicin, idarubicin, irinotecan, ixabepilones, nab-paclitaxel, topotecan, tretinoin, vindesine, vinflunine and vinorelbine. However, natural products can be used in the detection of cancer (Chanda et al. 2011).

The mammalian sialic acid N-glycolylneuraminic acid is metabolically incorporated from the dietary sources (e.g. - red meat and milk) into fetuses and some normal tissues. However, it is highly found in glycoproteins and glycolipids of human tumors. Thus, these kinds of cancer cells can be detected through the detection of N-glycolylneuraminic acid by using the immunohistochemical, enzyme-linked immunosorbent assay (ELISA), Western blot and flow cytometry analyses as well as affinity chromatography (Diaz et al. 2009).

Withaferin A, a steroidal lactone isolated from *Withania somnifera* is evident to target heat shock protein 90 (Hsp90) in human pancreatic (Panc-1) cancer cells (Yu et al. 2010). On the other hand, the nano system comprising of silica using bio-compounds extracted from the Mexican tree "Palo azul" (*Eysenhardtia polystachya*) are evident to incorporate into human breast cancer (MCF-7) cells (Ferreira et al. 2015). The conjugate compound of 2-aminoethyl diphenyl borateand 5,3',4'-tridemethylnobiletin (a unique polymethoxy flavone metabolite derived from citrus polymethoxy flavone) can be used to detect different biological samples, including floating cells, adherent cells, and animal tissues (Chen et al. 2015).

The bioaffinity technique, cell membrane chromatography is a widely used method for characterizing the interactions between drugs and membrane receptors, especially for complex samples such as herbal medicines. Baicalein, wogonin, chrysin, oroxylin A, neobaicalein and rivularin from *Radix scutellariae* were found to retain in human liver cancer (HepG2) cells (Jia et al. 2016). Moreover, the anthracyclines produced by actinobacteria are used effectively in the treatment of cancer, can be detected their levels in biological samples by using spectroscopic methods such as mass spectrometry. It should be mentioned that, the anthracyclines are toxic to their producers (Bauermeister et al. 2016). Thus, the detection of these drugs may be an application of controlling and monitoring the levels of anticancer drugs in surrounding normal cells.

Transferrin receptor is highly expressed in tumor cells. In a study, the binding capability of some phenolic compounds (twenty-five flavonol glycosides and eight phenolic acids) from the flowers of *Bauhinia blakeana* was detected by using HPLC-diode-array detector-multi-stage mass spectrometry-transferrin-fluorescence detector method (Liu et al. 2016). There is no doubt that, the breast cancer is one of the most lethal types of cancer in women worldwide due to the late stage detection and resistance to traditional chemotherapy. The human epidermal growth factor receptor 2 (HER2) is considered as a validated target in breast cancer therapy. The bioinformatics tools can be used to identify the novel effective HER2 inhibitors as well as monitor their efficacy. The structure-based virtual screening combined with the absorption, distribution, metabolism, excretion and toxicity is capable to monitor in this case. In a recent study, by using this tool, Li et al (2016) found ZINC15122021 (a natural compound) to inhibit the kinase activity against HER2 as well as presenting an outstanding cell proliferation inhibition activity against both SKBR3 and BT474 cell lines. Furthermore, streptavidin-magnetic nano-bead was demonstrated to detect the adenosine content in normal human urines and cancer patient urines, suggesting a reliable and sensitive adenosine detection method in the early clinical diagnosis and medical research (Feng et al. 2016).

The cone beam computed tomography as well as fluoroscopy can be used to detect the lipiodol (ethiodized oil, is a poppy seed oil used for cancer imaging) retention pattern in human hepatocellular carcinoma (HCC) cells (Hu et al. 2016). In a recent study, the natural product 4'-geranyloxyferulic acid and its conjugate with l-nitroarginine methyl ester were found to detect in mononuclear cells by applying the high-performance liquid chromatography (HPLC) technique (Taddeo et al. 2017).

Many synthetic substances such as hydrazine and sodium borohydride are used as powerful reducing agents in the synthesis of metallic nano-particles (Esumi et al. 2001). However, these reducing agents are highly toxic to the living organisms and to the ecosystem. On the other hand, the herbs and plants are the potential sources of antioxidants (Hoyoku et al., 2007). The uses of such kind of antioxidants in the diets and as medicaments are widely known to be non-toxic to the living organisms and to the environment (Holst and Williamson 2008). Recently, a number of phytochemicals have been employed for green 'nano-synthesis'; phytochemicals from soy, tea and cumin are some of the examples of them (Shukla et al. 2008; Katti et al. 2009; Nune et al. 2009). Chanda et al (2011) prepared cinnamon-coated gold nanoparticles (average diameter of 13 ± 5 nm) that had been internalized in normal human prostate (PC-3) and MCF-7, and prostate cancer (PC-3) cells. They observed that, the non-toxic cinnamon-phytochemical-coated gold nano-particles produced an excellent detectable photoacoustic signals from the internalized cancer cells than the normal PC-3 cells (Figure 1). Interestingly, the phytochemical-coated-nano-particles did not affect the relative cell viability in any cases.

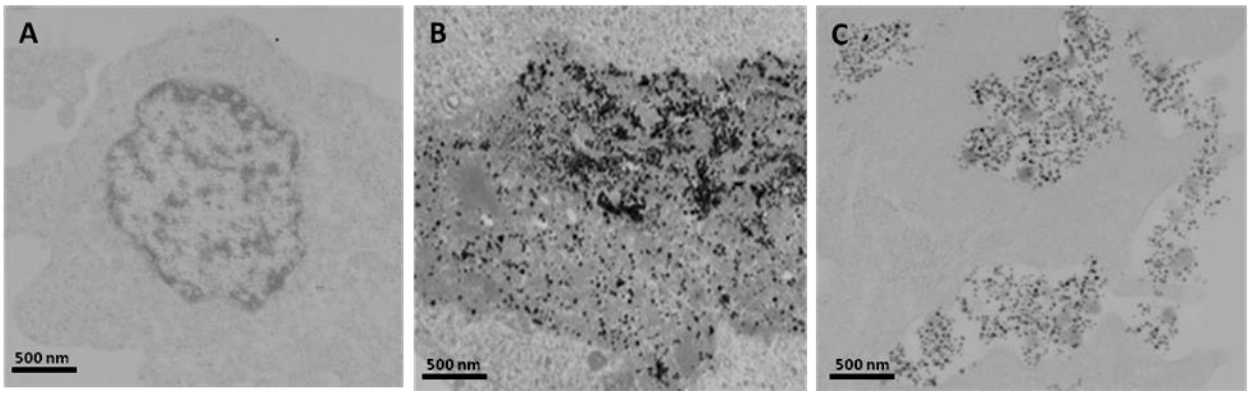

Fig. 1: Transmission Electron Microscopy Images Showing (A) Normal PC-3 (B) MCF-7 and (C) PC-3 Cells Internalizations of Cinnamon-Phytochemical-Coated Gold Nano-Particles. (Source: Chanda et al. 2011)

It should be mentioned that, the phytochemical constituents of cinnamon include: essential oils (1-4%), polyphenols (5-10%), carbohydrates (80-90%), and others such as gum, mucilage, resin and calcium monoterpenes oxalate. Among the essential oils, cinnamon contains aldehydes up to 60-80%, including trans-cinnamaldehyde (Mathew and Abraham 2006; Lopez et al. 2007; Shan et al. 2007). It seems, natural products of various chemical classes can be used in 'GREEN SYNTHESIS' as well as cancer cell detection. Moreover, natural products can be used to target genetic materials and can be monitored their activities there. For an example, the purine nucleoside phosphorylase activity is involved in cell survival and function. HPLC method can be used

for the determination of purine nucleoside phosphorylase activity in plasma (Giuliani et al. 2016).

3. Relevant perspectives

Natural products and their advanced preparations can be used not only for the treatment, but also monitoring the anticancer activity. For an example, catechin nanoemulsion (composition: catechin extract, lecithin, Tween 80, and deionized water; mean particle size: 11.45 nm) mediated inhibitory effect of human PC-3 cells was detected by using high-performance liquid chromatography-mass spectrometry method (Tsai and Chen 2016). In a recent study, celastrol (a quinonemethidetriterpene an abundant bioactive constituent of *Tripterygium wilfordii*) was used to detect RNA replication and protein synthesis of DENV via specific microRNA silencing and inhibition (Yu et al. 2017).

On the other hand, (-)-epigallocatechin-3-O-gallate-nanoethosomes (composition: 0.2% EGCG, 2% soybean phosphatidylcholine, 30% ethanol, 1% Tween-80 and 0.1% sugar esters) were investigated as a preventative treatment for human melanoma (A-375) cells, where the transdermal delivery of the nanopreparation was used to monitor the tumor growth (Liao et al. 2016). In another study, Capistrano et al (2016) demonstrated that, *Gloriosa superba* extracts (0.3-3.0 mg/kg) rich in colchicines and colchicoside prepared as a putative pro-drug, when administered in pancreatic tumor (PANC02)-bearing C57BL/6 mice for 10 successive days, significantly reduced the Ki-67 scores and relative tumor volumes. In this study, positron emission tomography imaging using 2-deoxy-2-[^{18}F]fluoro-d-glucose (^{18}F-FDG) was used to detect the *in vivo G. superba* extracts uptake profile and overall cancer progression. Moreover, artesumycin, a fluorescent hybrid of the natural products marmycin A and artemisinin was found to inhibit the cancer cell proliferation through an iron-dependent manner, which was visually detected by using fluorescence microscopy (Mariani et al. 2016).

As a cancer treatment strategy, in many cases, surgery is followed by the radiotherapy. However, the radiotherapy exerts a number of complications, including cancer treatment mediated a secondary cancer. Borda Rodríguez and AnduezaIriarte (2016) suggested that rosehip oil can be used to prevent epithelitis in the patients with head and neck cancer treated by intensity modulated radiotherapy.

Vaccines, the biological preparations are designed to promote tumor specific immune responses. However, other cancer treatment strategies such as surgery and ablation, chemotherapy, and radiotherapy, can also induce antitumor immunity, thereby having cancer vaccine effects. In this regard, the monitoring of patients' immune responses at the baseline and after standard of care treatment is shedding light on immune biomarkers (Butterfield et al. 2015). Photodynamic therapy can be used in the management of various cancers. However, the sensitivity towards light of any natural product should be considered, as photo-induced alteration of the substance, especially the plant-derived drugs can induce cell death via different mechanisms, including apoptosis, necrosis, autophagy, cell cycle regulation and even the regulation of various cell signaling pathways (George and Abrahamse 2016).

Doubtless, the anticancer drug-induced toxicities and the management are two burning questions. Therefore, after administration, the drug concentrations need to maintain in an appropriate range to be effective. Furthermore, the drug dosage defined during the clinical studies may be inappropriate for the individual patient due to differences in drug absorption, metabolism and excretion profiles. Thus, the therapeutic drug monitoring is an important challenge in cancer chemotherapy. According to Crotti et al (2015) mass spectrometry-based methods can be used for pharmacokinetic quantification of anticancer drugs in biological samples, especially those are derived from natural origin. Moreover, Khoogar et al (2016) also demonstrated that, the natural products are capable to reduce off-target toxicity of therapeutics with the continuation of on-targeting the cancer cells.

4. Conclusion

The application of natural products is immense and charismatic. From the accumulated evidences, this text says that, the natural products can be applied for the detection of cancer cells along with the treatment, and monitoring of the cancer therapy as well as cancer progression. However, more researches are necessary concerning to the toxicological effects on normal cells in each application. In fact, each natural product has a number of pharmacological effects on its producers as well as towards other biological systems.

5. Conflict of interest

None declared.

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